

### REMARKS

Claims 1-2, 4-38 and 40 are currently pending. Claim 1 is amended herein to clarify the claimed subject matter. Claims 9 and 10 are canceled herein without prejudice. Accordingly, instant claims 1-2, 4-8, 11-38, and 40 are under consideration.

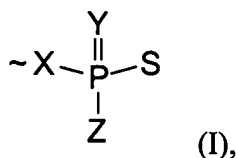
Any amendment, however, is not to be construed as abandonment of any subject matter of the originally filed application. Accordingly, it is to be understood that Applicant reserves the right to reintroduce subject matter deleted from the application by the foregoing amendments and to file one or more divisional, continuation, and/or continuation in part applications directed to such subject matter.

Support for amendment to the claims is found throughout the specification and in the original claims. More particularly, support for amendment to claim 1 is found, for example, in original claims 9 and 10 and at paragraphs [0017] and [0040] of specification US2007/0269806, which corresponds to the instant application. No issue of new matter is introduced by these amendments.

### ***Rejections under 35 USC § 102***

Claims 1-2, 4-9, 15, 18-20, 23-34, 37, 38, and 40 are rejected under § 102(b) as allegedly anticipated by Zhao et al (Nucleic Acids Research, 2001, Vol. 29, No 4, 955-959). Claim 1 is amended herein to clarify the subject matter of the claim. Claim 9 is canceled herein, thereby obviating any rejection of this claim. In view of the clarifying amendments to the claims and arguments presented herein, this rejection is respectfully traversed.

More particularly, claim 1 is amended herein to be directed to a hairpin polynucleotide, having a loop and a stem region, characterised in that the hairpin polynucleotide comprises a sulfur-based nucleophile, wherein the sulfur-based nucleophile is a moiety of the formula (I):



wherein ~ denotes a linker connecting the sulfur-based nucleophile to the remainder of the polynucleotide; X represents an oxygen atom, a sulfur atom or a group NR, in which R is hydrogen or an optionally substituted C<sub>1-10</sub> alkyl; Y represents an oxygen or a sulfur atom; and Z represents an oxygen atom, a sulfur atom or an optionally substituted C<sub>1-10</sub> alkyl group, and wherein the sulfur-based nucleophile is attached to the base of an internal nucleotide or to the 1'-carbon atom of an abasic internal nucleotide in the hairpin through a linker to enable binding to a solid support. Thus, the instant hairpin polynucleotide comprises a sulfur-phosphorus linkage attached to the nucleoside base or to 1'-carbon of an abasic nucleotide where the nucleoside has no base. In contrast, Zhao et al. teach a hairpin functionalized through the phosphate backbone between the nucleosides. In that the instant claims are amended to specify that the hairpin polynucleotides of the present invention possess features that are not taught or suggested by Zhao et al., namely a hairpin polynucleotide that comprises a sulfur-phosphorus linkage attached to the nucleoside base or the 1'-carbon atom of an abasic nucleotide, Applicant asserts that Zhao et al fails to anticipate the claimed molecules.

In view of the amendments to the claims and Applicant's arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 1-2, 4-9, 15, 18-20, 23-34, 37, 38, and 40 under 35 U.S.C. §102 and withdraw the rejection.

### ***Rejections under 35 USC § 103***

Claims 1-2, 4-9, 11-12, 15-38, and 40 are rejected under § 103(a) as allegedly unpatentable over Balasubramanian et al. (U.S. Patent Application Serial Number 2003/0022207) in view of Zhao et al. (Nucleic Acids Research, 2001, 29:955-959). Claim 9 is canceled herein, thereby obviating any rejection of this claim. It is noteworthy that the Office Action indicates that claims 10, 13 and 14 are directed to allowable subject matter if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Accordingly, claim 1 is amended herein to incorporate the allowable subject matter of claim 10 regarding abasic nucleotides and the subject matter of claim 9. Claim 1 now specifies that the sulfur based nucleophile is attached to the base of an internal nucleotide or to the 1'- carbon atom

of an abasic internal nucleotide in the hairpin through a linker to enable binding to a solid support. Thus, the claim now specifically requires that the sulfur based nucleophile is positioned on the end of a linker. In view of the clarifying amendments to the claims and arguments presented herein, this rejection is respectfully traversed.

As detailed above, claim 1 is amended herein to clarify that the claimed hairpin polynucleotides are thiophosphate modified hairpins, wherein the thiophosphate moiety/moieties are positioned on the end of a linker. Neither Balasubramanian et al. nor Zhao et al., when considered alone or in combination, teaches or suggests a thiophosphate modified hairpin, wherein the thiophosphate moiety/moieties are positioned on the end of a linker as presently claimed. In light of the above, the combined teachings of the cited references fail to teach or suggest each and every element of the hairpin polynucleotides of claim 1 and, therefore, fail to render obvious the instant claims.

Moreover, the absence of any guidance in these references relating to thiophosphate modified hairpins, wherein the thiophosphate moiety/moieties are located on the end of a linker underscores a total lack of appreciation regarding any potential advantages of positioning a thiophosphate moiety in such a manner. As previously detailed by Applicant, the Zhao et al. reference describes attachment of hairpin stem-loop structures with multiple phosphorothioate moieties in the loop to a solid support. The Examiner acknowledges this structural limitation of the hairpin oligonucleotides of Zhao et al. by describing the oligonucleotides as modified with multiple phosphorothioates in their backbone. As further described therein, the phosphorothioate groups in the hairpin loops of Zhao et al. are utilized as means for direct attachment to the surface. There is, however, no suggestion in Zhao et al. to indicate that the use of a separate linker to connect the phosphorothioate group to the polynucleotide can improve the efficiency of the initial covalent coupling reaction that couples the hairpin polynucleotide to the chemically functionalized solid support. The teachings of Balasubramanian et al., moreover, fail to remedy this deficiency.

As stated by Applicant in the previously filed Response, the experimental results of the present invention reveal that the efficiency of attachment of thiophosphate modified hairpin

polynucleotides to a solid support is dramatically improved when the thiophosphate moiety is attached through a linker rather than simply placed in the backbone chain of the polynucleotide. The difference in coupling efficiency is clearly depicted in Figure 2 of the instant application. Moreover, the discovery that the novel hairpin nucleotides of the present invention possess substantially enhanced attachment efficiency was surprising. See, for example, the Summary and Examples of the present specification.

In light of the above, the combined teachings of Balasubramanian et al. and Zhao et al. fail to teach or suggest a recited feature of the instantly claimed hairpin polynucleotides and furthermore, fail to demonstrate any appreciation of the surprising and useful properties conferred by this feature. More particularly, the combined teachings of Balasubramanian et al. and Zhao et al. fail to provide any guidance relating to the claimed hairpin polynucleotides, which are thiophosphate modified hairpins wherein the thiophosphate moiety/moieties are positioned on the end of a linker attached to the nucleoside base or to the 1'-carbon atom of the abasic nucleoside. These references also fail to teach or suggest that the claimed thiophosphate modified hairpins, wherein the thiophosphate moiety/moieties are positioned on the end of a linker, would possess a novel and surprising functional property, namely improved coupling efficiency to a chemically functionalized solid support. That being the case, the combined teachings of Balasubramanian et al. and Zhao et al. fail to teach each and every element of the instant claims and functional properties conferred by inclusion of such elements and, therefore, would not lead an ordinarily skilled practitioner to the presently claimed invention.

In view of the amendments to the claims and the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 1-2,4-9, 11-12, 15-38, and 40 under 35 U.S.C. §103 and withdraw the rejection.

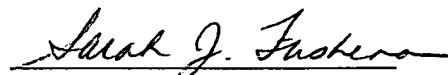
### ***Fees***

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

***Conclusion***

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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